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Long Term Testolactone Therapy for Precocious Puberty in Girls with the McCune-Albright Syndrome

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ABSTRACT

We used the aromatase inhibitor testolactone (40 mg/kg·day) to treat 12 girls with precocious puberty due to the McCune-Albright syndrome for periods of 0.5–5 yr. In the 7 girls who received testolactone for at least 3 yr, the mean ± SD serum estradiol level was 618 ± 268 pmol/L at the start of therapy and fell to 156 ± 84 pmol/L at 1 yr, 116 ± 48 pmol/L at 2 yr, and 241 ± 260 pmol/L at 3 yr ($P < 0.05$ compared to the start of therapy), with recurrent ovarian cysts at 3 yr in 2 patients. These 7 girls averaged 8 menses/yr before therapy. The average frequency of menses decreased to 2 episodes/yr during the first year of treatment, 3/yr during the second year, and 4/yr during the third year. The mean ± SD testosterone levels were slightly above the normal prepubertal range (0.51 ± 0.2 nmol/L) before treatment and did not change significantly during treatment. The mean ± SD androstenedione levels rose from 1.1 ± 0.6 nmol/L before treatment to 2.1 ± 0.1 nmol/L at 2 yr and 2.8 ± 0.1 nmol/L after 3 yr of treatment ($P < 0.05$ compared to before treatment) and were consistent with normal adrenarche. The mean predicted adult stature was 143.0 ± 7.8 cm before treatment and 147.3 ± 11.5 cm at 3 yr (P = NS). In 3 of 12 girls, all with bone age greater than 12 yr, the gonadotropin responses to LHRH indicated early central precocious puberty after 1–4 yr of treatment. The adverse effects of testolactone were transient abdominal pain, headache, and diarrhea in 3 girls and elevated hepatic enzymes in 1 girl who had abnormal liver function before treatment. Six families acknowledged difficulty in adhering to the daily dosing schedule. We conclude that testolactone can be effective in the treatment of LHRH-independent precocious puberty in girls with McCune-Albright syndrome, but that some patients exhibit an escape from the effects of treatment after 1–3 yr. (*J Clin Endocrinol Metab* **77:** 647–651, 1993)

THE MCCUNE-Albright syndrome (MAS) presents in its classic form as polyostotic fibrous dysplasia, café-au-lait skin pigmentation, and endocrine hyperfunction. These abnormalities have recently been linked to the presence, in affected tissues, of activating mutations of the α-subunit of the stimulatory G-protein component of the cAMP signal transduction system (1). MAS is characterized by a LHRH-independent form of precocious puberty; thus, the long-acting analogs of LHRH, which are used to treat LHRH-dependent precocious puberty, are not effective in the early stages of the condition (2, 3). We have previously reported the effectiveness of testolactone, an aromatase inhibitor that blocks the conversion of androgens to estrogens, in the short term (6 month) treatment of 5 girls with MAS (4). Here, we report the results of testolactone treatment for up to 5 yr in 12 girls with MAS.

Subjects and Methods

Subjects

The patients were referred to the NICHHD for the evaluation of precocious puberty. The diagnosis of MAS was based upon the classical clinical findings, the presence of ovarian cysts, and suppressed or prepubertal LH and FSH levels after LHRH treatment. The presence of polyostotic fibrous dysplasia was confirmed in all girls with technetium bone scan and/or conventional radiographs. Nine of the 12 girls had café-au-lait skin pigmentation, and 6 also had the thyroid abnormalities associated with this syndrome (5).

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The patients' mean ± SD age at the start of treatment was 4.7 ± 1.9 yr, and their mean bone age (BA) was 8.6 ± 2.6 yr (Table 1). The mean ± SD height (+1.53 ± 2.2) and growth rate (+2.7 ± 1.9) SD scores (SDS) were elevated compared to those in normal girls of the same age. Due to the wide range in the severity of bone disease, the stature of some subjects, such as patients 10 and 12, and the growth rate of others, such as no. 3 and 8, were below the normal mean, despite their advanced BAs.

The short term results of testolactone treatment in patients 1–4 have been reported previously (4). These patients initially underwent a 6-month trial of testolactone, followed by a 6-month period without treatment. Testolactone was then reinstituted and continued without interruption for 3–5 yr. For the current study, the baseline data for these four patients before therapy were obtained from the 6-month period without treatment.

Treatment protocol

To minimize the diarrhea and cramping that may occur early in treatment, testolactone was increased at weekly intervals from 10 mg/kg·day to a final dose of 40 mg/kg·day, orally, divided into every 6 h doses.

Evaluations

Patients were admitted to the Clinical Center at the NIH. Informed consent was obtained from a parent, and assent from the patient, where appropriate. Evaluations were performed at 6-month intervals. Plasma levels of estradiol (E_2), androstenedione (A), and testosterone (T) were measured at 1000, 1400, 2200, and 0200 h. LH and FSH were measured after the administration of 100 μg LHRH, iv, at 0800 h. Ovarian volumes were calculated, from pelvic ultrasonography data, according to the formula: volume = length × width × thickness × 0.52 (6). The mean ovarian volume (MOV) denotes the mean of the volumes of the right and left ovaries. When one ovary was absent as a result of a previous ovariectomy, the MOV represented the volume of the remaining ovary. Predicted adult height was estimated according to the method of Bayley and Pinneau (7). LH (8), FSH (9), E_2 (10), A (11), and T (12) were

TABLE 1. Clinical characteristics of 12 girls with MAS at the start of long term testolactone therapy

Patient no.	CA (yr)	BA (yr)	Ht (cm; SDS)[a]	Growth (cm/yr; SDS)[a]	Pubertal stage (Br/PH)	Café au lait pigment	Bone disease[b]	Thyroid disease[c]	Previous therapy	Duration of testolactone therapy (yr)
1	5.1	10.5	120.8 (+2.5)	8.55 (+1.8)	III/I	No	+	No	LHRH-A[d]	3.0
2	7.0	11.0	142.7 (+3.9)	8.80 (+3.2)	III/III	No	+	No	LHRH-A	3.0
3	5.3	12.0	125.0 (+3.3)	7.00 (−0.5)	IV/III	Yes	+++	A, B, D	LHRH-A	3.0
4	5.3	10.0	128.3 (+3.8)	8.30 (+1.7)	IV/III	Yes	++	No	LHRH-A	5.0
5	4.3	7.8	109.2 (+1.0)	8.30 (+1.4)	II/I	Yes	+	A, D	None	5.0
6	2.7	5.8	99.7 (+2.0)	12.70 (+3.0)	IV/II	Yes	++	A, C	Ovarian cystectomy	4.0
7	4.0	7.8	105.5 (+1.2)	13.50 (+5.0)	II/II	Yes	++	A, B, E	None	3.0
8	7.8	11.8	135.4 (+2.0)	5.60 (−0.3)	IV/II	Yes	+++	No	None	1.5
9	7.2	10.5	136.3 (+2.5)	9.54 (+4.0)	II/IV	No	+	No	Provera	0.9
10	2.8	5.8	91.6 (−0.2)	16.30 (+5.0)	III/I	Yes	+++	A, C, E	None	1.0
11	3.5	5.0	99.3 (+0.3)	12.70 (+4.1)	II/I	Yes	++	No	Ovariectomy	1.0
12	1.8	5.0	76.6 (−4.0)	18.60 (>+4.0)	IV/II	Yes	++	A	None	0.5

[a] Compared to normal girls of comparable CA.
[b] +, Mild; absence of facial assymetry, limb length discrepancy, or gait abnormality; ++, moderate; obvious facial/skull assymetry, limb length discrepancy, no fracture or corrective surgery, +++, marked; as in moderate, but with fracture and/or need for surgical correction.
[c] A, Suppressed TSH. B, Goiter. Ultrasonographic findings: C, inhomogeneity; D, hypoechoic areas (cysts); E, hyperechoic areas (nodules).
[d] The long-acting LHRH analog DTrp^6,Pro^9-Des-Gly^{10}-LHRH ethylamide.

measured by previously described methods. The detection limits for the assays were 0.3 IU/L (LH and FSH), 75 pmol/L (E_2), and 0.35 nmol/L (A and T).

Statistical analysis

The hormonal and growth data of patients 1–11, who were treated for at least 0.9–1 yr, were compared after 1 yr with the corresponding observations before treatment. The data in patients 1–7, who were treated for at least 3 yr, were then compared after 1, 2, and 3 yr of testolactone treatment.

The hormone and ovarian volume data for each 12-month period of treatment were the mean of the two 6-month measurements made during that period. The rates of growth and BA advance [ΔBA/ΔCA (chronological age)] were determined at 12-month intervals.

The frequency of menses, determined from parental reports, was expressed as episodes per yr. The pretreatment value represents the annualized frequency based upon a 6-month observation period.

The data are presented as the mean ± SD, except where stated otherwise. Statistical analysis of hormonal and growth data was performed by one-way repeated measures analysis of variance with *post-hoc* comparisons, using a computerized statistics program (Statview, Abacus Concepts, Inc., Berkeley, CA). Analysis of frequency of menses was performed using a nonparametric repeated measures test (Friedman test); *post-hoc* comparisons were made using a signed rank test (Wilcoxon test) with the Bonferroni correction.

Results

Patients 1–11

The mean serum E_2 level was 543 ± 315 pmol/L before treatment and 154 ± 81 pmol/L at 1 yr ($P < 0.01$). The MOV was 6.9 ± 5 mL before treatment and 5.1 ± 4 mL at 1 yr (P = NS). The growth rate SDS was 2.9 ± 1.7 before treatment and 1.1 ± 1.6 after 1 yr ($P < 0.05$). The ΔBA/ΔCA was 1.8 ± 4 before treatment and 1.45 ± 0.8 at 1 yr (P = NS). Menses stopped at 1 yr in 5 of the 10 girls (no. 1, 4, 5, 8, and 10) who had menses before treatment, and in 3 subjects (no. 2, 3, and 6), they decreased in frequency.

Peak LH was 4.5 ± 3 and peak FSH was 4.1 ± 4 IU/L before treatment; at 1 yr, LH was 7.4 ± 6, and FSH was 6.9 ± 6 IU/L (P = NS). The LH and FSH responses to LHRH rose to the pubertal range in patients 8 and 9 (peak LH, 21.5 and 36.4 IU/L; peak FSH, 15.4 and 13.9 IU/L, respectively) when their BAs were 12 and 12.5 yr. Patient 8 continued testolactone treatment, with the addition of a LHRH agonist to control central puberty. Patient 9 refused further treatment.

Patients 1–7

E_2 and MOV (Figs. 1 and 2). The mean plasma E_2 levels were significantly lower after 1, 2, and 3 yr compared to those at the start of therapy ($P < 0.05$). The apparent increase and greater variability in E_2 at 3 yr resulted from elevations of plasma E_2 in patients 1 and 3 (592 and 653 pmol/L, respectively).

Although there was a decrease of approximately 50% in the MOV at 1 and 2 yr, this did not achieve statistical significance. At 3 yr, the MOV increased, primarily due to unilateral cysts in patients 1 and 3 (MOV, 9.1 and 37.0 mL), which reappeared simultaneously with a rise in the E_2 levels, and to bilateral ovarian enlargement (MOV, 15.0 mL) in patient 4, which was found even though a concomitant rise in E_2 was not detected. In patients 2 and 4–7, E_2 was at least 55% below the pretreatment levels throughout their course of treatment, although the MOV continued to fluctuate (range, 0.8–15.0 mL).

A and T (Fig. 3). A levels rose from 1.1 ± 0.6 nmol/L before treatment to 2.1 ± 0.1 nmol/L after 2 yr and 2.8 ± 0.1 nmol/L after 3 yr ($P < 0.05$), which is consistent with normal adrenarche (13). Levels of T were slightly above the normal prepubertal range before treatment (0.51 ± 0.2 nmol/L) and did not change during treatment. No girl exhibited acne, hirsutism, or virilization during treatment.

Rates of growth and bone maturation (Table 2). The growth rate SDS during treatment was lower at all time points than that at the start of therapy, although this achieved statistical significance only at 1 and 3 yr. Patient 3, who had severe progressive bone disease, lost height during her treatment and was not included in this analysis. The mean ΔBA/ΔCA

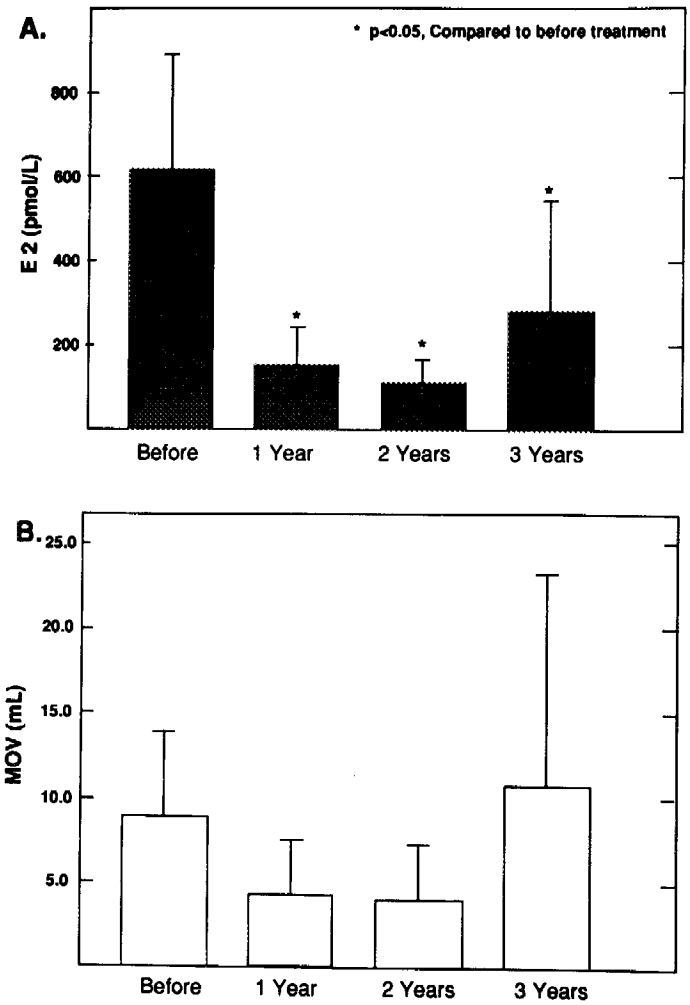

FIG. 1. Mean ± SD serum E_2 (A) and MOV (B) in girls with MAS before and after 1, 2, and 3 yr of testolactone treatment. *, $P > 0.05$ compared to before treatment.

also fell progressively during treatment, although this decrease was significant only at 3 yr.

Predicted adult stature (Fig. 4). Predicted adult stature increased slightly over the 3-yr course of therapy from 143.0 ± 7.8 to 147.3 ± 11.5 cm, but did not achieve statistical significance. Two of the three patients (no. 3 and 5) who had a decrease in predicted adult stature had progressive bone disease and femoral fractures.

Menses and pubertal staging. Patients 1–6 reported regular episodes of menses before treatment (annualized mean, eight per yr), whereas patient 7 was premenarcheal. After 1 yr of treatment, three of seven girls reported menses (average, two per yr; $P < 0.03$ compared to before treatment); after 2 yr, four of seven girls reported menses (average, three per yr; $P < 0.03$); and after 3 yr, five of seven girls reported menses (average, four per yr).

Before treatment, pubertal stage ranged from II-IV (breast) and I-III (pubic hair). Patients 3, 4, and 6 had transient regression in breast stage during the first 6–12 months of treatment; the other patients had either no change in pubertal stage or a gradual progression in stage over their treatment course. By 3 yr, stages were III-IV (breast) and II-V (pubic hair).

LH and FSH responses to LHRH. The LH and FSH responses to LHRH rose to the pubertal range (14) after 3 yr of treatment in patient 7 (peak LH, 30.8; peak FSH, 12.8 IU/L) when her BA was 12 yr. The other six girls continued to have suppressed or prepubertal LH and FSH responses after LHRH treatment, including patients 1, 3, 4, and 5, whose BAs were 14–15 yr by the end of treatment.

Discontinuation of therapy

Therapy was stopped in patients 1–5 when their ages were close to those for normal puberty. In addition, patients 1 and 3, who had elevated plasma E_2 levels and MOVs, appeared to have become unresponsive to testolactone. Patients 2 and 5 discontinued treatment somewhat earlier than planned (CA, 9.1 and 9.5 yr; BA, 13.3 and 14.0 yr, respectively) because the parents had difficulty in maintaining the dosing regimen and requested that testolactone be stopped. Patient 7 remains on testolactone together with a LHRH agonist. Patient 10 developed elevated E_2 (463 pmol/L), MOV (16 mL), menses, and a growth spurt after 1 yr. Her family denied noncompliance, and she was considered a treatment failure. Patient 11 exhibited markedly elevated E_2 (1420 and 9474 pmol/L) and MOV (32 and 60 mL) on two occasions after testolactone was stopped independently by the family. She had no clinical symptoms other than vaginal bleeding every 3 months. Testolactone was discontinued at parental request. No other patient exhibited a comparable rebound of E_2 and MOV after stopping treatment.

Patient 12, who has been the subject of a previous study (1), had failure to thrive (height, −4 SD despite an advanced BA) and elevated hepatic enzymes before treatment. This patient experienced a further elevation of hepatic enzymes after 3 months of testolactone treatment, with persistent menses, anemia, and increased rate of bone maturation. Testolactone was discontinued, and she was treated with bilateral ovariectomy. No other patient had hepatic enzyme elevation attributable to testolactone treatment. The only other adverse effects were mild diarrhea and cramping in three patients (no. 1, 2, and 9), which responded to a temporary reduction in dose. Two patients (no. 5 and 9) complained of headache during treatment; however, both also had areas of active polyostotic fibrous dysplasia in the base of the skull and maxilla.

Discussion

This long term pilot study of testolactone in girls with MAS showed that testolactone was effective in suppressing serum E_2 levels and frequency of menses for 1–3 yr in many girls. However, two patients (no. 10 and 12) did not respond to treatment, and two (no. 1 and 3) exhibited a recurrence of cyst formation and elevated E_2 levels after 1–3 yr of continuous treatment.

Decreased compliance could have caused unresponsive-

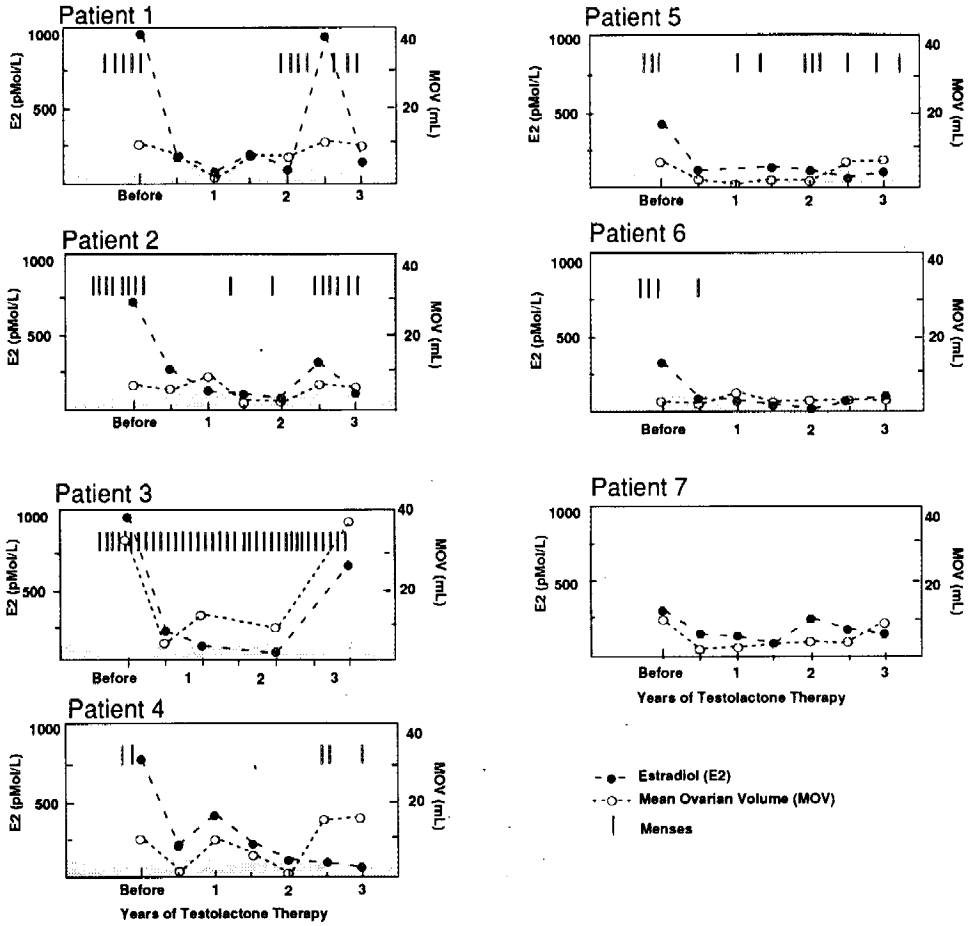

FIG. 2. Serum E_2 levels (●), corresponding MOV (○), and episodes of menstrual bleeding (*vertical bars*) in patients 1–7 before and during 1, 2, and 3 yr of testolactone treatment. The *shaded regions* are below the detection limit of the E_2 assay (75 pmol/L).

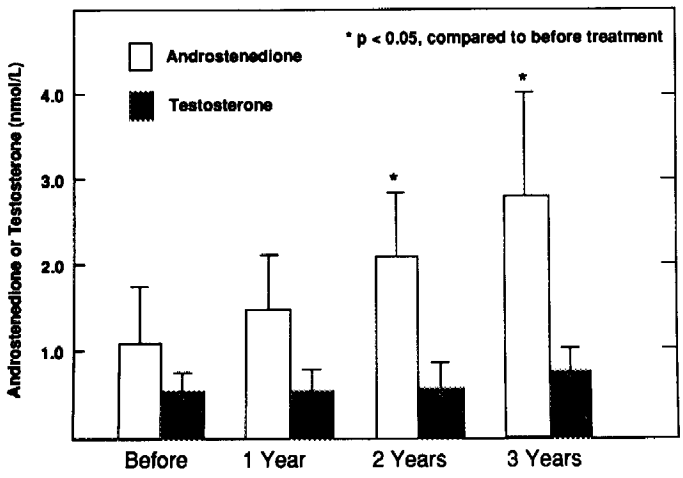

FIG. 3. Mean ± SD A and T levels in girls with MAS before and after 1, 2, and 3 yr of testolactone treatment. *, $P < 0.05$ compared to before treatment.

ness to treatment in these patients, and when surveyed, six families acknowledged that the dosing schedule had been difficult. Only one patient's family (2) said that more than 10% of the doses had been missed.

Secondary LHRH-dependent precocious puberty could also explain late treatment failure. This phenomenon has

TABLE 2. Mean ± SD growth rate SDS and rate of bone maturation (ΔBA/ΔCA) in girls with MAS before treatment and after 1, 2, and 3 yr of testolactone treatment

	Before treatment	Treatment		
		1 yr	2 yr	3 yr
Growth SDS	2.9 ± 1.4	0.66 ± 1.6[a]	1.03 ± 1.8	0.78 ± 2.0[a]
ΔBA/ΔCA	2.0 ± 0.3	1.43 ± 0.7	1.10 ± 0.7	0.39 ± 0.2[a]

[a] $P < 0.05$ compared to before treatment.

previously been reported in girls with MAS (15), in boys with familial male precocious puberty (16), and in children with congenital adrenal hyperplasia (17). During our initial 6-month trial of testolactone treatment (4), we observed an increase in the peak LHRH-stimulated LH and FSH levels from below normal to levels that approached those in normal prepubertal girls and hypothesized that prolonged treatment might result in a further rise of gonadotropin levels into the pubertal range. Although the long term data showed a rising trend in serum gonadotropin levels, only three girls met hormonal criteria for central puberty. Gonadotropin levels remained below the pubertal range in the remaining patients, including those whose BA advanced beyond 14 yr.

It was not possible to correlate responsiveness to treatment with disease severity because of the varied expression of the disorder in this small group of patients. Furthermore, the lack of a significant improvement in predicted adult height

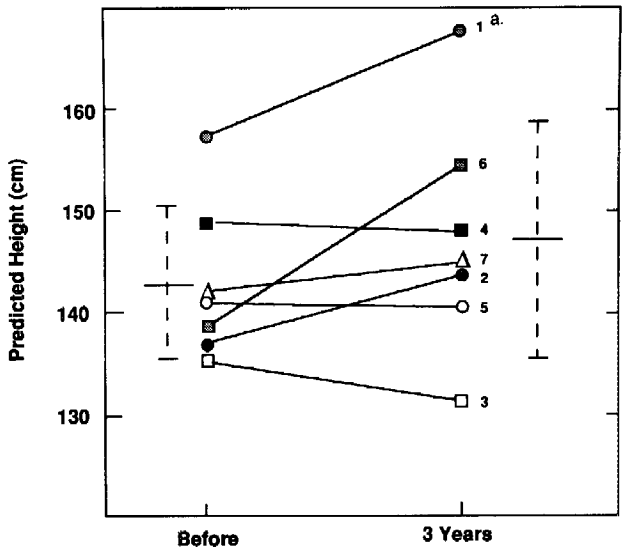

FIG. 4. Predicted adult stature in patients 1–7 before treatment and after 3 yr of testolactone. a, Patient no.

in many girls does not necessarily indicate lack of efficacy in suppressing estrogen biosynthesis, since in MAS, short adult stature results from both early epiphyseal fusion and the sequelae of the bone disease.

We conclude that many girls with MAS appeared to benefit from long term testolactone treatment, as reflected by decreased serum E_2 levels, decreased frequency of menses, and slowed rates of maturation. Nevertheless, signs of puberty persisted in many patients. We hypothesize that this was due to incomplete inhibition of estrogen production. Newer aromatase inhibitors, with greater potency and a longer half-life, could be expected to effect a more satisfactory clinical response.

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